IMPROVING THE CONDUCT OF ENVIRONMENTAL EPIDEMIOLOGY STUDIES

PHASE I OF A THREE-PHASE REPORT

Major Issues in the Development of Guidelines or Criteria
for the Conduct of Environmental Epidemiology Studies
Based on a Review of 17 Environmental Health Reports
of the Massachusetts Department of Public Health

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Background

In the fall of 1986, the Massachusetts Department of Public Health (DPH) contracted with the Occupational Health Program of the University of Massachusetts Medical School to perform the first phase of a three-phase project to assist the Department in determining when and what type of epidemiologic studies should be performed in response to suspected environmental health problems in the state. The goals of the three phases of this project are:

Phase I - To review 17 environmental epidemiology reports of the Department in recent years in order to determine their strengths and weaknesses and to define issues necessary for development of guidelines or criteria to determine when and what types of epidemiologic studies should be performed on suspected environmental health problems (by December 31, 1986).

Phase II - To develop the guidelines or criteria (by April 30, 1987).

Phase III - To make recommendations to the Department on improving surveillance systems and interagency relationships in order to better identify, investigate, and control environmental health problems (by June 30, 1987).

Phase I Methodology

The Occupational Health Program assembled a team of four physicians with both epidemiology and environmental health training and experience, and a doctor of science epidemiologist with expertise in occupational and environmental epidemiology. We reviewed 17 environmental epidemiology reports that were selected and supplied by the Department (see Table). The reports were discussed at a series of meetings in the final quarter of 1986. The remainder of this document consists of a review of these reports, focusing on shortcomings and areas where improvement is needed as well as a discussion of the major issues for the development of the epidemiologic guidelines that emerged directly from this review.

A REVIEW OF 17 DPH REPORTS

The table at the back of this report gives some basic information on the reports reviewed. We divide the review of the 17 reports into three general categories: the conception or design of the investigations, the methodology used, and the interpretation of the results presented in the reports. Our comments pertain strictly to the written reports that were provided, and not to any other materials that DPH might have produced or received during the course of its investigations. Community response and DPH follow-up to these reports, while critically important, was not within the scope of this contract.

1. CONCEPTION

A. Problem Definition

In the 17 reports reviewed, it was often unclear what the problem of concern to the community or DPH had been. One or two reports summarized the chain of events which led to the performance of a study, but this was the exception rather than the rule. In our opinion, each report should include, at its outset, a summary of the public health concerns which motivated the investigation. The lack of background information made it difficult to evaluate how well the reports had addressed the concerns of the communities involved in most cases. We also recognize that in some cases problems can be defined by observations made by health officials during routine surveillance. A description of the problem definition process is especially important in these cases.

B. Statement of Hypothesis

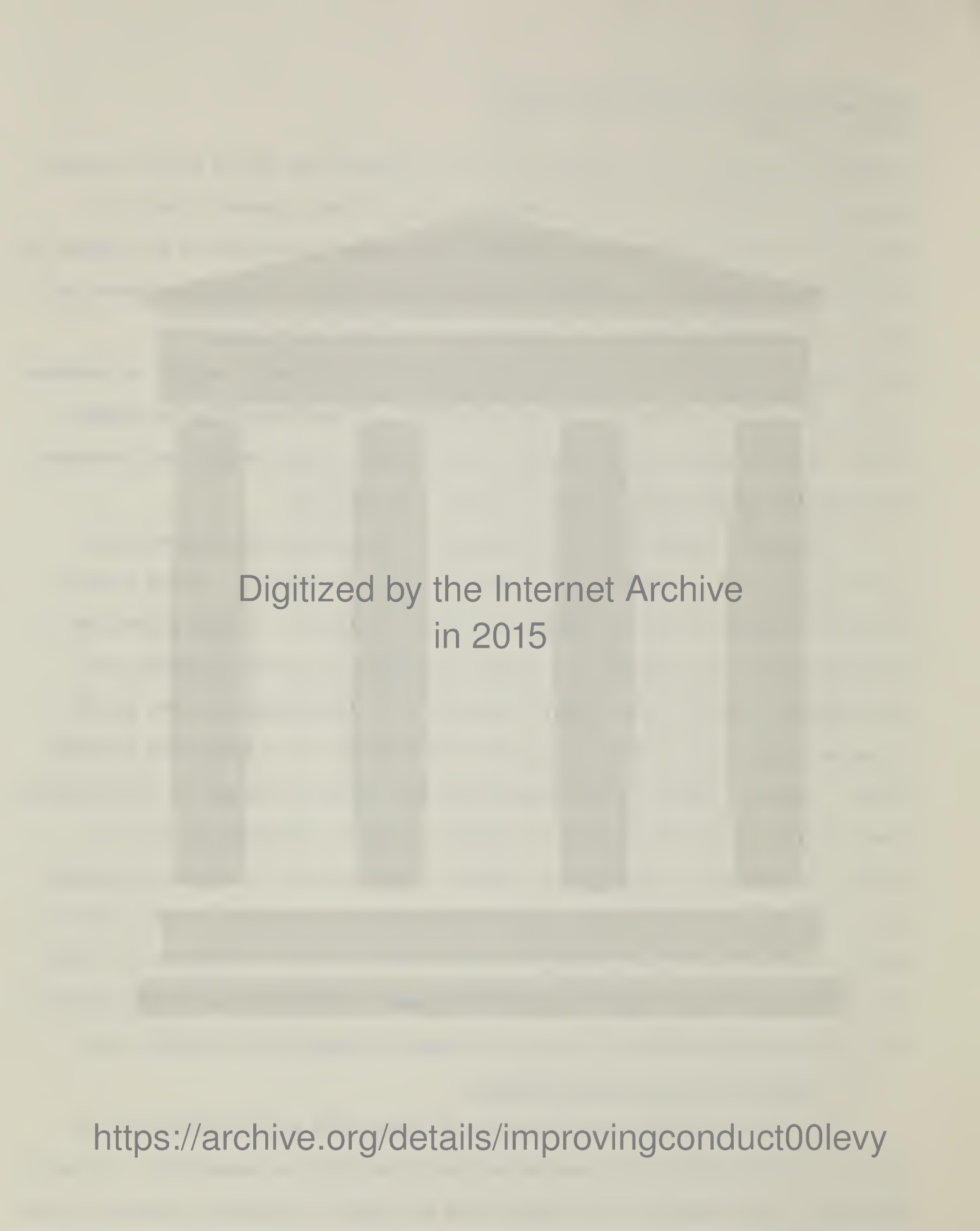
The reports reviewed rarely contained a clear hypothesis (see "Types of Data" in Table). A statement of a scientific hypothesis is not only an essential part of any

investigation but it is also different from a summary of the public health concerns referred to in Section A. By this concept, we do not mean a formal statistical construct of null and alternative hypotheses but rather a statement of the problem in terms that are amenable to study with the resources of DPH. Community concerns may not be well focused or may not be expressed in the form of an hypothesis. Nevertheless, any investigation should be based on an hypothesis, and it is important for the scientific validity of the investigation that this hypothesis be clearly stated. Such an hypothesis also enables the public to decide whether the Department's investigation has addressed the same concerns that they have.

An essential component of an hypothesis for an environmental epidemiologic investigation is a consideration of potential routes of exposure. In the reports reviewed, potential routes of exposure are rarely mentioned. In many situations, a potential source of pollution in a community appeared to be the motivation for a investigation. Cancer rates in this community were then analyzed to look for an increased risk of some cancer which might have been due to the identified pollution source. However, without an hypothesis about how community exposure to pollutants may have occurred, it is not possible to properly evaluate this potential risk. In several of the reports, there was an implicit assumption that the route of exposure from, for example, a toxic waste dump to the community was via air. Such a route of exposure raises significant issues about wind patterns and the dispersal of a plume from a site, but these issues were rarely discussed. Obviously, an entirely different set of considerations would arise were the route of exposure via drinking water.

C. Statement of Appropriate Response

The reports reviewed rarely provided any information which would assist the reader in understanding why a particular kind of analysis was undertaken. The health department should explain to the reader what the range of potential responses are and



why a particular response was chosen. This is also an opportunity for the health department to explain the limitations that prevent it from doing a more extensive study on every problem that arises. This section would not need to be extensive but might refer to a standard protocol as a justification for the level of response that was taken. Clearly, community education is an important component of this activity.

2. METHODOLOGY

A. General

The presentations of methodologies used in the 17 reports examined were erratic and inconsistent. A standard format should be followed. This format would summarize the sources of data for both health outcomes and environmental pollution levels, and the analytic methods used. Any statistical terminology used should be explained clearly in lay language. In particular, there seemed to be considerable confusion about the meaning of a negative study and of a finding that was not statistically significant.

B. Exposure assessment

The studies rarely presented any environmental data, yet this kind of information is critically important in many DPH studies. A number of problems which are presented to DPH may not be important enough to warrant extensive environmental monitoring. However, a simple review of existing environmental data would improve many studies and would force a clarification of the hypothesized route of exposure by which a pollutant of concern might have caused the health problems that DPH is investigating.

C. Epidemiologic methods

Even though a quick analysis of existing data might not be thought of as a real study, it should be, because even the simplest analysis should contain all of the major elements of epidemiologic design principles. Epidemiologic studies need not be complex to be appropriate and of high quality; however, they must be clearly designed

and accurately performed. Since the design of appropriate studies depends upon details of the problem at hand, the following are general statements about important features of epidemiologic investigations.

Every epidemiologic study must include a clear case definition. A clear explanation of the methods of case ascertainment is equally important. DPH studies frequently utilize mortality or incidence data which are derived from large computerized data bases. The definitions employed in these data bases were not designed to provide case definitions for all conceivable cluster investigations. For example, if there is a suspicion of a cluster of leukemia cases, the inclusion of various types of leukemia in the case definition must be carefully considered.

It is equally important to state clearly how the selection of a control group was made. When studies are performed using existing data, it is easy to forget that a control group was chosen. Often in these studies, the control group was the entire Massachusetts population. This is appropriate for some kinds of studies; however, DPH should consider making more frequent use of smaller and more carefully designed control groups; one example is the use of cases of other types of cancer when doing a study of a specific cancer type in a community. By drawing both cases and controls from the statewide cancer incidence registry, it is often possible to perform an inexpensive and quick study that could be more focused and sensitive than the standard study of a particular community, recognizing there are limitations with such an approach.

A majority of these 17 investigations appeared to be looking for a cluster of cancers occurring in a population at risk residing near a particular pollution source in a town. However, these studies rarely defined the geographic or temporal limits of the population at risk. Most commonly the cancer mortality or incidence rates in a particular census tract or town were calculated. These were compared to another town

or adjoining census tract. While it may often be necessary to use census tracts for these investigations because they are the smallest level for which data are available, this approach should always be used with caution; the hypothesized route of exposure might project a population at risk that does not coincide with political boundaries. Geographic clustering was also often investigated by presenting a map of the community on which the residence of the patients with cancer and the environmental hazard were both located. The comments about these maps usually stated that no geographic clustering was evident. However, without a clear statement of the route of exposure it is impossible to evaluate the validity of this conclusion. Furthermore, no information was ever presented on the population density in the areas on such maps. Without this information, it is impossible to evaluate whether a particular geographic distribution of cases shown is different from what would be expected, based on where people live in the community.

The temporal boundaries of the population at risk is an equally important concern. If these boundaries are defined incorrectly, a false negative or a false positive conclusion about the existence of a disease cluster can result. For example, if a community reports a cluster of concern over a two-year period, a DPH analysis can easily confirm an elevated incidence over two years, even if this actually represents a random variation in cancer occurrence in the population, which would be discovered if a longer time frame were used. Even populations exposed to carcinogens at a single point in time (e. g., Hiroshima) manifest excess cancer risk over an extended period. Again the studies may well be limited to investigations of time periods for which data are available. But simply because data are not available does not mean that a problem does not exist. This distinction is often blurred in DPH reports.

Temporal relationship between the hypothesized exposure and the disease of concern must also be fully explored. DPH should not simply accept the time frame of

those who have brought a potential cluster to the Department's attention. In many reports there is no discussion whatsoever of the potential temporal relationship between exposure and disease. In a few studies of cancer rates, there was a discussion of the problem of cancer latency; but DPH could do more to apply latency concepts as a way of anchoring study conclusions to basic principles of cancer biology. Latency considerations may eliminate certain observed cancer excesses due to lack of biological plausibility.

There is practically no discussion in any of the reports reviewed of the concept of statistical power. It is essential for the public and for DPH epidemiologists and decision-makers to recognize the limits that exist within the data available to them. Calculation of the power in a planned study design sheds important light on these limitations. In performing environmental epidemiologic investigations, one is continually running into the limits of weak and sparse data. DPH should always discuss these limitations in its studies. Several studies seem to confuse the absence of evidence of an effect with evidence of absence of an effect.

3. INTERPRETATION

An assessment of the interpretation of these studies is difficult because of the absence of clear information on the concerns of the community. In several of the studies, there is an attempt to interpret all data available to the investigators, regardless of how inconclusive the information might be. In contrast, other studies (Woburn, for example) included an analysis of the problems associated with using small numbers of cases collected from small populations.

A. Environmental data

As mentioned before, most of the DPH studies reviewed lacked assessment of

environmental data. In several situations, a presentation of existing environmental data and a statement of the meaning of that data might have been a sufficient response to the community's concern. Even if detailed survey information was not available, the usefulness of the mapping of cases in a geographic area would be greatly increased by information about sources of water, prevailing winds, etc., as addressed in the Norwood study. In the Norwood study, environmental data were presented, and appropriately used to indicate that significant exposure from a contaminated site was highly unlikely. The fact that environmental data suggest that pollution levels are below threshold limits should not be used to mechanically conclude that no problem exists, without a full discussion of the plausibility of alternative routes of exposure. Moreover, threshold limit values were not developed to define safe levels for the general population. It would appear that in many situations, DPH could simplify its tasks by presenting environmental data and then arguing that no reasonable route of exposure is apparent by which the pollution source of concern in the community could be expected to cause the excess cancers that may also have appeared in the tumor registry. In any case, a statement of the DPH conclusion regarding the presence or absence of a real health risk should be in every report if the environmental data appear sufficient for drawing a conclusion.

B. Health Effects Data

One of the most serious methodologic shortcomings in the 17 reports reviewed was the misuse of tests of statistical significance. The alpha probability level of .05 appears in these reports to be an absolute dividing line between a true association and no association. Even this incorrect assumption is confused by conflicting and incorrect explanations of the meaning of a p value. Epidemiologic studies should explore relationships which exist in the data and present these relationships to the

public and to decision-makers. The data themselves cannot automatically decide what is or is not a problem. The data only support or argue against particular hypothesized associations, in keeping with standard epidemiologic practice. DPH should calculate confidence intervals for each effect estimate that it presents and should honestly discuss what this confidence interval means. Standard epidemiologic analysis recognizes that a p value greater than .05 or analogously a confidence interval which includes a relative risk of 1.0 does not necessarily indicate that no association exists. DPH often appears to use a p value greater than .05 as a way of explaining away a potential problem.

There appears to be a misunderstanding about the meaning of age standardization. For example, high cancer rates in census tracts are sometimes linked to the presence of a high number of elderly persons in the tract and disregarded, despite the fact that the cancer rate was age standardized.

Often DPH reports a high rate of cancer mortality or incidence in a particular time period, but also finds that in earlier or later time periods no such elevation is evident. Sometimes this leads to the conclusion that a real problem does not exist but at other times a seemingly similar pattern of elevated risks leads to a conclusion that continued surveillance is needed and that implicitly the elevation may indeed be real.

Generally a discussion of lifestyle risk factors such as smoking is only brought into the reports to explain the occurrence of a "significant" excess of cancer. The absence of a systematic application of lifestyle risk factor analysis in all studies may lead some readers to conclude that these factors were simply being used to "explain away" the positive findings in the study.

C. Conclusions

The conclusions of the DPH studies generally lacked consistency and clarity. The explanation of "statistically" significant findings was often confusing. In addition, recommended control measures sometimes seemed inconsistent with the DPH report assessment of the seriousness of the hazard. The conclusions generally also lacked a frank discussion of the limitations of the studies performed. DPH can make its task easier if it can educate the public about the limitations of the studies that it is capable of performing.

Summary of Limitations in the Reports

The major correctable deficiencies in the 17 DPH reports can be summarized as follows:

1. Conception.

The development of a strong epidemiologic approach to a potential community health problem depends most of all upon a logical and relatively precise conception of the problem. The formation of scientific hypotheses, which are specified in as much detail as possible, provides the only basis for the application of scientifically valid methods. Even in preliminary analyses where the information about the problem is sparse, the investigators must first make various assertions and then determine how well the data support these assertions.

2. Methodology.

A variety of methodologic deficiencies were noted in the reports. As mentioned above, every investigation DPH undertakes must incorporate certain aspects of a full epidemiologic study. These include an explicit study design that speaks to the hypothesis under investigation, and an explanation in lay language of the statistical analyses being performed.

3. Interpretation.

Epidemiologic analyses of small clusters of disease in communities will often be inconclusive. The daily pattern of human lives rarely produces exposure situations that lend themselves to classical experimental analyses, and it distorts the scientific value of the epidemiologic approach to stretch the interpretation of these analyses very far. The only reasonable response to an inconclusive analysis is to clearly state the inconclusiveness, give arguments as to the reasons inconclusiveness occurred, and delineate the sorts of changes in method or data that might be required to overcome it. The DPH, given its role in protecting public health, has no choice but to master a knowledge of the limitations of its analyses and master the ability to communicate this knowledge to the public.

While these deficiencies can be addressed in future studies, we recognize that the Department will likely need to continue to operate in the face of certain "real world" constraints that pose limitations for such studies. These constraints include:

1. Affected or "at risk" populations that are small in numbers and may be difficult to define;
2. Difficulty in identifying control or comparison populations;
3. Lack of adequate exposure assessment data;
4. Affected populations possibly experiencing symptoms without objective clinical signs of illness;
5. Confounding factors, such as smoking or workplace exposures;
6. The route(s) of exposure by which a contaminant reaches an affected population may not be apparent.

IDENTIFICATION OF MAJOR ISSUES IN DEVELOPMENT OF GUIDELINES OR CRITERIA

What Problems Should Be Studied

Phase II of this project will consist of the development of guidelines to assist the Department in determining which suspected environmental health problems should be studied and what types of studies should be performed. Review of the 17 environmental health reports provided by the Department is only somewhat helpful in this regard because we did not receive information on what situations were not studied.

Basically, determination of what should be studied hinges on initially available exposure and health effects information as well as apparent or possible linkages between the two. Sometimes, even unsubstantiated clues may lead to useful investigations and preventive actions.

Considerations arising from the exposure information are:

1. Inherent toxicity of the material;
2. Plausible route(s) of exposure;
3. Number of people exposed;
4. Vulnerability of exposed people (e.g., children or the elderly);
5. Duration of exposure;
6. Intensity (level) of exposure and difference from normative or expected levels; and
7. Precision, reliability, and timing of exposure measurement and the competency/expertise of the individual(s) performing the measurement.

Considerations concerning the health effects information are:

1. The seriousness of the health effect;
2. The number (and rate) of people affected;

3. Differences of observed disease rates from those expected (statistical tests included); and

4. Validity of data.

What Types of Studies Should Be Performed

The initial response by the Department to a community concerned about a suspected environmental health problem should always include a statement of DPH's understanding of how the problem is perceived by the community. The next step would be for the Department to frame the problem in the form of a scientific hypothesis, which is a prerequisite to any systematic investigation. If there is agreement that the hypothesis mirrors the community concern, then work can go forward. If not, it needs to be modified so that it does. In some cases the community's concern may not be of such a form that it can be rigorously framed. The solution in this instance is to work with the community to clarify its concerns, not to investigate an irrelevant or untestable hypothesis.

Initial evaluation focuses on obtaining and analyzing already existing data, usually both health effects and exposure data. Existing health effects data for cancer, for example, will usually include primarily cancer mortality information (from death certificates) and cancer morbidity information (from the State Cancer Registry). Basic epidemiologic analyses of these data can yield important guidance as to whether to proceed with further investigation or not. Existing exposure information will ordinarily come from the Massachusetts Department of Environmental Quality Engineering and Department of Labor and Industries (Division of Occupational Hygiene) and the Federal Environmental Protection Agency and Occupational Safety and Health Administration.

Additional analyses and investigations will be guided by the conclusions from the initial assessment of information already available.

Options for further health effects studies include:

1. More sophisticated analyses of existing morbidity and mortality data.

DPH currently has available to it cancer incidence and mortality data, and data on adverse reproductive outcomes in Massachusetts. These data can be the basis for a variety of different types of studies. Phase II of this project will present a variety of options for the full use of DPH's existing data resources.

2. Case-control studies.

When studying small regions such as towns or neighborhoods in which an excess risk of a particular disease is suspected, a case-control study should be considered. The cases might be identified from the tumor registry and the control or referent population might consist of another tumor series from the tumor registry, or perhaps healthy residents of the area under study selected from the town books. Cases and controls are then compared for the relative frequency of various exposures, such as residence near a suspected source of environmental pollution. Such studies need not be expensive or time-consuming, particularly since the cases (and possibly controls) can be readily identified from the tumor registry.

3. Cluster analyses.

The investigation of geographic and temporal clustering of cases of disease requires specific statistical methodology, and several procedures are available for doing this analysis. Some of the methods are not difficult and do not require sophisticated computer programs or high-powered mathematics. DPH should adopt a small number of these statistical

tools and employ them when there is reason to suspect small cancer clusters arising from environmental hazards.

Options for further exposure information include:

1. Data on levels of environmental contamination and potential routes of exposure may be obtained by DEQE or other environmental agencies through sampling of water, air, or soil.
2. DPH may sample "at-risk" individuals to measure body burdens of environmental contaminants in an exposed population.
3. Additional information on groundwater movement, prevailing local wind patterns and occupational sources of contaminants may be requested from appropriate sources.

Beyond this, there should be a standard approach to determining if long-term follow-up studies should be done and, if so, what types of studies are warranted.

Considerations for Future Phases

We recognize that the resources of DPH are limited and that work needs to be prioritized. Our Phase II report will be developed in order to assist the Department in setting such priorities.

Existing surveillance systems will be reviewed in Phase III of this work, and suggestions will be made as to how they might be improved to assist with the determinations about which we are concerned.

In addition, in Phase III we will review existing interagency cooperative activity with regard to these studies and make recommendations on how interagency cooperation (DPH with DEQE, for example) might be improved.

ACKNOWLEDGEMENTS

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TABLE: S

MAJOR

	TITLE	ISSUE[1]	HEALTH EFFECTS
1	A Report on Cancer Mortality in Adams. July 13, 1984	Apparent community concern over cancer on two streets of town.	Cancer mortality data.
2	An Analysis of Mortality in the Neighborhoods of Boston: 1979-1982. August 1985	Death from the 3 leading causes in the neighborhoods of Boston.	Mortality data.
3	Childhood Leukemia in Fairhaven. June 28, 1982.	Leukemia cases near Cushman Park, park flooded by PCB-contaminated river.	Cases of leukemia ascertained from Board of Health and newspaper reporter
4	Epidemiologic Analysis: Holbrook, with Addendum. July and December 1985.	Possible health effects of the Baird and McGuire toxic waste site.	Cancer incidence and mortality, adverse reproductive outcomes.
5	Hodgkin's Disease in Leominster. July 13, 1983.	Board of Health concerned about Hodgkin's Disease, an environmental cause suspected.	Cases from "area tumor registries".
6	Review of Cancer Incidence and Environmental Data for Quinsigamond Village in Worcester. May 1, 1986.	Not stated-apparent community concern over a chemical company.	Cancer incidence data.
7	Lexington Breast Cancer Incidence and Mortality. May-September, 1985.	Not stated-concern over breast cancer in and around Lexington.	Breast cancer incidence and mortality.
8	PCB Exposure Assessment in Norwood. February 22, 1984.	PCB-contaminated lot adjoining residential area.	Serum PCB level determination.
9	An Investigation into Pancreatic Cancer Mortality in Peabody. June, 1984.	Community concern about pancreatic cancer, possibly related to Pierpont St. Park	Dead cases identified from "state heal statistics".
10	Salem High School Hodgkin's Disease Investigation. June 27, 1984	Apparent high rate of Hodgkin's Disease at Salem High School.	Cases of Hodgkin's Disease reported from school principal.
11	Cancer Mortality in Sheffield. July 18, 1984.	Not stated--citizen concern over cancer mortality.	Cancer mortality data.
12	Leukemia and Lymphoma Mortality in Shrewsbury: 1979-1983. May 17, 1985.	Community concern over alleged waste site contaminating water	Leukemia incidence and mortality data.
13	Sulresim Area Health Study: Report of Finadings. November 22, 1983.	Community concern over possible health effects from Silresim site.	Community health survey, mortality da
14	Cancer Mortality in Templeton (1969-1982). July 5, 1984.	Not stated-cancer mortality in Templeton.	Cancer mortality data.
15	A Review of Cancer Incidence and Mortality and Birth Outcome Data for Bourne, Falmouth, Mashpee, and Sandwich. September 18, 1985 and addendum.	Community concern.	Cancer mortality and incidence data, adverse reproductive outcome data.
16	Woburn: Cancer Incidence and Environmental Hazards: 1969-1978. January 23, 1981 and August 27, 1984.	Community concern over childhood leukemia.	Cases of leukemia.
17	A Report on Cancer and Infant Mortality in Whately. June 22, 1984.	Cancer mortality; not further specified	Cancer mortality data. Neonatal mortality data.

NOTES:

1. Represent the reviewers' interpretation based solely on the information in the reports. 2. Standardized Mortality Ratio Study.

MMARY OF REPORT DATA

TYPES OF DATA

EXPOSURE ASSESSMENT	MAJOR TYPES OF ANALYSIS	MAJOR RESULTS/CONCLUSIONS
None.	SMRs[2] for 3 time periods and for town census tracts.	Cancer mortality in Adams similar to statewide rates.
None.	SMR, and directly standardized. rates.	Charlestown and S. Boston have high rates of heart disease and cancer.
DEQE radiation survey mentioned but not included in analysis.	Not well-described. Case-series without reference population data.	Not clearly stated. Apparent excess childhood leukemia rate.
None.	SMR, SIR[3], comparison of reproductive outcomes to unexplained expected numbers.	Some excess cancer mortality; cancer incidence and adverse reproductive events at normal levels.
Questionnaire data on exposure of cases.	Case series, calculation of incidence rate and comparison to U. S. rate.	Excess incidence of Hodgkin's Disease with no cause identified.
DEQE air monitoring.	PIR[4]	Excess lung cancer incidence. No health hazards found in air monitoring data. Recommend air pollution control equipment.
None.	SMR, SIR[4]	Unclear. Excess breast cancer mortality?
Questionnaire to determine time spent in area.	Comparison of serum PCB level with reported exposure.	No significant PCB exposure.
Questionnaire data on exposures of cases, air and water pollution data.	Case series, SMR by census tract.	"..pancreatic cancer mortality..is probably not related to living in Peabody."
Questionnaire data on exposures of cases.	Case series, calculation of incidence rate.	Excess incidence of Hodgkin's Disease with no cause identified.
None.	SMR	No excess cancer mortality in Sheffield.
None.	SMR, mapping of cases.	"..no relationship between the alleged wastesite...and the incidence of leukemia and lymphoma"
DEQE environmental data.	Multivariate models for numerous diseases and complaints.	No increased cancer or adverse reproductive outcomes, but increased reporting of various health complaints.
None.	SMR, mapping of cases.	"No specific type of cancer was significantly elevated in Templeton".
None.	SMR, PIR, comparison of reproductive outcomes to expected numbers.	Excess cancer mortality of various sites, no excess reproductive outcomes.
Questionnaire data on exposures of cases, DEQE environmental data not incorporated into study.	Case control study, SIR	Excess leukemia incidence. No environmental exposure identified as a cause.
None.	SMR	No excess cancer mortality.

3. Standardized Incidence Ratio Study 4. Proportional Incidence Ratio Study.